Retinopathy of Prematurity: Incidence and Severity in Hawaii

John H. Drouilhet MD, Susan Pelke RN, Donald Sroat MD
Malcolm Ing MD, Byron Wong MD, Gregg Kokame MD and David Easa MD

Because survival of low birth-weight infants requiring intensive care has improved recently, particularly since the advent of exogenous surfactant therapy, we reviewed our experience at Kapiolani Medical Center for Women and Children (KMCWC) from 1989 to1991 to determine if the incidence of retinopathy of prematurity (ROP), a serious long-term complication, had also increased. During this 3-year period, threshold disease, the ROP stage in which cryosurgery is recommended, occurred only in infants ≤1000 grams. Seventy-four infants ≤1000 grams were diagnosed with ROP of any stage. Sixteen eyes (9 infants) reached threshold; 14 were treated with cryosurgery. Six of these eyes have useful vision on follow up; 8 do not. Exogenous surfactant therapy had no significant effect on ROP incidence or severity in our series. Although ROP incidence did not increase during this review period, it remains a serious problem in high-risk premature infants in our Newborn Intensive Care Unit.

Introduction

Retinopathy of prematurity (ROP), a disorder of altered retinal vasculature occurring frequently in low birth-weight infants requiring neonatal intensive care, can result in visual disability or permanent blindness. This condition is thought to be unpreventable, although it has been found to be related to 2 major factors: Birth weight and the duration of oxygen exposure.[1,2,3,4,5] Retinal vasculature changes occur over time and can progress through a sequence of stages leading to permanent blindness. During this progression, the retinal vasculature reaches a threshold at which point the disorder might be amenable to surgical intervention, indicating the need for frequent and repeated ophthalmologic evaluations.[5,6]

Departments of Surgery and Pediatrics
Kapiolani Medical Center for Women and Children
and John A. Burns School of Medicine
University of Hawaii, Honolulu

Correspondence to:
David Easa MD
Kapiolani Medical Center for Women and Children
1319 Punahou St., Honolulu HI 96826
(808) 973-8670

Submitted for publication: July 30, 1993

Nationally, the survival of infants requiring neonatal intensive care has improved over the last decade;[7,8,9] this also is true for infants treated in Hawaii.[9,10] Newer treatments, such as exogenous surfactant therapy for the most common, serious pulmonary disorder of prematurity, Respiratory Distress Syndrome (RDS), have contributed significantly to this improved survival.[11] As a result, the number of infants surviving with birth weights <1000 grams and gestational ages <26 weeks has increased. This study questioned whether improved survival of low birth-weight infants would be accompanied by a higher incidence of long-term complications such as ROP.

Accordingly, this is a retrospective review of KMCWC's recent experience with infants who developed ROP in the first 3 years after exogenous surfactant therapy was initiated in the Newborn Intensive Care Unit (NICU). This study focused on infants ≤1000 grams birth weight, since these tiniest infants have the highest risk of death and disability.

Materials and methods

Retrospectively the charts were reviewed of infants with a diagnosis of ROP who were discharged from the NICU between January 1, 1989 and December 31, 1991. Demographic information, including birth weight, gestational age, days in oxygen, days on mechanical ventilation and surfactant treatment was collected.

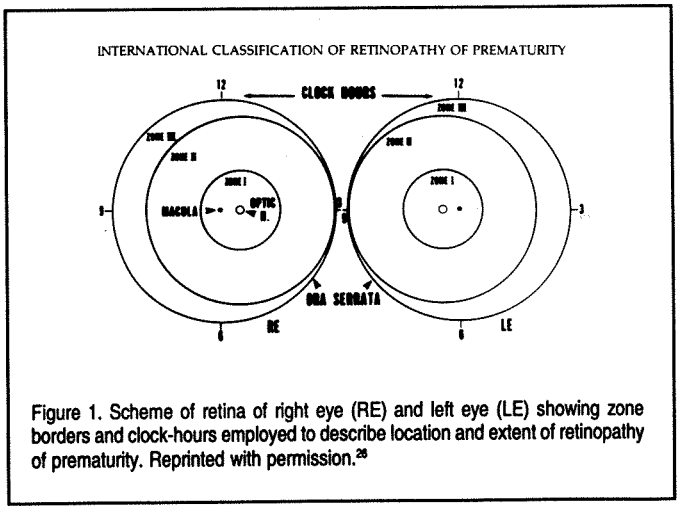

Figure 1. Scheme of retina of right eye (RE) and left eye (LE) showing zone borders and clock-hours employed to describe location and extent of retinopathy of prematurity. Reprinted with permission.[26]

ROP Classification: ROP was defined according to the International Classification of Retinopathy of Prematurity, which has standardized the anatomic evaluation of the disorder. This classification describes the abnormalities of retinal development based on location, extent of the disease and staging.[12]

ROP is reported as being located in Zone I, Zone II, and Zone III. During gestation, normal retinal vasculature grows from the optic disc outward to the periphery of the retina anteriorly in the eye. Zone I describes a radius extending from the optic nerve to twice the distance of the disc to the center of the macula. Zone II extends in a radius from the optic disc to the nasal ora serrata and temporally to the equatorial area. Zone III includes the area anterior to Zone II extending to the ora serrata temporally (Figure 1). The extent of the disease is expressed in clock-hours of involvement. These clock-hours are described as the observer looks at that eye.

Staging of the disease ranks the severity of abnormal vasculature from Stages I to V. Stage I involves a flat white demarcation line separating vascularized from avascular retina with abnormal branching of retinal vessels. In Stage II, the line becomes a ridge and extends away from the retinal surface. The ridge contains extraretinal fibrovascular proliferation into the vitreous in Stage III (Figure 2); this criterion is necessary to define threshold disease when considering cryosurgery. Stage IV is retinal detachment as the result of exudates or traction; Stage IV-a describes no macular involvement, while Stage IV-b includes macular detachment. Stage V is total retinal detachment.

Plus disease designates increasing dilation and tortuosity of the retinal vessels with vessel engorgement in the iris, poor pupillary dilation and vitreous haze (Figure 3).

Threshold disease is defined as Stage III Plus disease in Zone II with greater than 5 contiguous or 8 noncontiguous hours of extraretinal fibrovascular proliferation. Zone I with Plus disease is also considered threshold for treatment with cryosurgery.

Analysis of Data: Our data were analyzed for normality of distribution with the goodness-of-fit test. Normally distributed groups were compared for significance using the student's t-test; the Mann-Whitney test was used for non-normally distributed groups. Chi square analysis was used to test proportional data; a p value of <0.05 was considered significant. Values are expressed as means ± standard error.

Results

There were 1,288 admissions during the review period. Four infants were excluded from the review because they were transferred from other facilities and their records were not complete. Another infant was deleted from the analysis involving surfactant because it was unknown whether or not she had received surfactant during the extended follow-up required.

From 1989 to 1991, 87% of all NICU admissions had birth weights >1000 grams* and 88% of these survived.** Thirty (3%) of these infants developed ROP. This group of larger ROP infants had a mean birth weight of 1326±64 grams; 83% weighed <1500 grams. Mean gestational age was 29±0.4 weeks; only 3 infants were >31 weeks old. Stage III pre-threshold was the most severe stage reached; this developed in only 3 eyes. No eyes reached threshold or required cryosurgery.

In the group of infants 1000 grams, 167 were admitted* during this 3-year period; 119 survived to discharge.** Of these surviving infants, 74 (62%) were diagnosed as having ROP. The incidence rate remained stable during the review period, ranging between 60% to 64% in each of the 3 years that were studied.

The severity of ROP was related inversely to birth weight; threshold or greater stages were found only in infants ≤1000 grams. The exceptions were the 2 surviving infants with birth weights <500 grams born during this period. Although both had mild ROP, neither reached threshold level. Overall, of the 74 infants ≤1000 grams with ROP, 16 eyes (9 infants) reached threshold level and 14 eyes were treated with cryosurgery; the parents declined bilateral cryosurgery in each of twins. Demographic data for this group of infants included mean birth weight of 775±14 grams and gestational age of 26.3±0.2 weeks. They required oxygen for 76±4 days and ventilator therapy for 37±3 days. The only deaths in this ROP group during this 3-year period occurred in 3 infants who weighed <750 grams.

Sixty-one of the above infants with ROP also received surfactant therapy for RDS during this 3-year period; 48 of these were

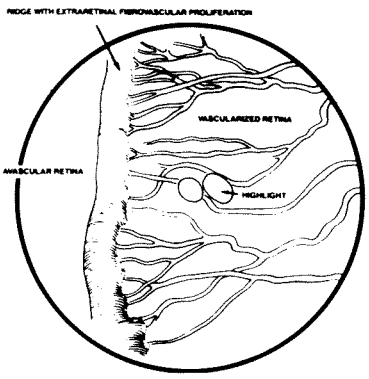

Figure 2. Line drawing of extraretinal fibrovascular proliferative tissue of Stage III. Reprinted with permission.[26]

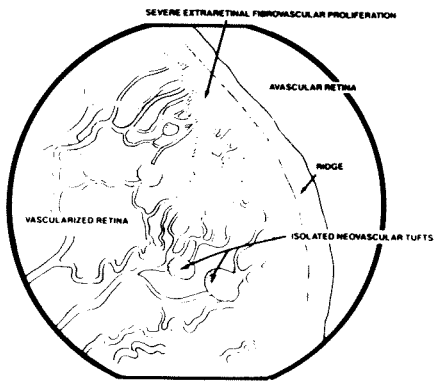

Figure 3. Line drawing of extraretinal fibrovascular proliferation of amounts of tissue judged to be characteristic of severe Stage III. Reprinted with permission.[26]

≤1000 grams. There were various inclusion and exclusion criteria for surfactant administration, although most infants with documented RDS received surfactant therapy, leaving no untreated controls. Nevertheless, our review found 25 infants ≤1000 grams who did not meet the criteria for being given surfactant and were similar in many respects to the surfactant-treated infants. This non-surfactant group was comprised of infants with mean birth weight of 780±30 grams and mean gestational age of 26.2±0.3 weeks who required 77±11 days in oxygen and 39±8 days on mechanical ventilation. None of these parameters was significantly different from their surfactant-treated counterparts.

The number of eyes reaching threshold level was similar between the surfactant– (n=9) and non-surfactant– (n=7) treated infants ≤1000 grams. Seven eyes in each group required treatment with cryosurgery. There were 3 deaths in the non-surfactant group, but none in the surfactant group ($p = 0.01$).

The outcome of the 14 eyes treated with cryosurgery was determined by follow-up of 1 to 4 years. Of the 14 eyes undergoing cryosurgery, 6 eyes have useful vision and 8 eyes have no functional vision. Of the 8 eyes with no useful vision, 6 were attributed to retinal detachment, 1 to a significant macular fold and 1 to severe temporal dragging of the macula. Only one of the 6 eyes with useful vision had a normal appearance. The other 5 had mild temporal dragging of the vessels and/or macula. Five of the 9 infants treated with cryosurgery had received surfactant. Seven eyes were treated in these 5 infants; 3 eyes (43%) have no useful vision. Of the 4 infants not receiving surfactant, 7 eyes had cryosurgery but 4 (57%) have no useful vision.

Discussion

This retrospective review demonstrated that 62% of NICU survivors with birth weights ≤1000 grams had ROP. The results suggest the incidence of ROP, including the percent of infants reaching threshold or worse, is similar to reports from other neonatal intensive care units in this country[1,5,13] and around the world.[2]

Our results further indicate that exogenous surfactant therapy did not have any significant effect on the incidence of ROP or on its severity in this small series. This conclusion is based on a comparison between a group of infants receiving exogenous surfactant therapy and a similar group not treated with surfactant. While these untreated infants cannot be considered controls, the groups were nevertheless similar enough to allow for this conclusion. Our data is in agreement with a general consensus from other studies reporting the incidence of ROP in various large surfactant trials.[14,15,16,17,18,19,20,21] However, Repka et al retrospectively reviewed 112 low birth-weight infants receiving prophylactic surfactant treatment with Infrasurf and demonstrated that such therapy was associated with a decreased incidence of ROP.[22]

Available published follow-up data from surfactant-treated infants 1 and 2 years later are so far anecdotal and inconclusive. A review of 1,450 infants at one year of age indicated that the incidence of visual deficits (41 compared with 36) and blindness (13 compared with 12) was only slightly increased in control infants compared to those treated with surfactant.[23] In a series of 35 infants at 14 months adjusted age, Ferrara et al found 2 treated infants and 1 control infant who were blind as a result of ROP.[24] In another review[25] at 2 years of age, 2 of 39 surfactant-treated infants were blind while none of 33 controls were blind.

Although our small cohort makes it difficult to draw significant conclusions, we have demonstrated that retinopathy of prematurity continues to be a serious problem in high-risk premature infants requiring NICU care at KMCWC. Infants with serious ROP were those ≤1000 grams. Sixty-two percent of survivors in this weight group had ROP; 12% of these infants (11% of affected eyes) had threshold disease. Forty-three percent of the eyes of infants undergoing cryosurgery could fix and follow; the others had no useful vision. Exogenous surfactant therapy did not have an impact on the incidence or on the severity of ROP in our cohort.

Although the pathogenesis of ROP is poorly understood, a number of multicenter clinical trials currently are underway to determine the value of various new therapeutic interventions applying both oxygen and light in order to determine the potential benefit in reducing the incidence of ROP.

Footnotes
* 31 infants admitted in 1989 were excluded because medical records not accessible.
** 1 additional infant of unknown birth weight died and was excluded.

References

1. Phelps DL. Retinopathy of prematurity. In: *The micropremie: the next frontier.* Report of the 99th Ross Conference on Pediatric Research. Ross Laboratories, Columbus, Ohio, 1990;134-145.
2. Gallo JE, Lennerstrand G, Broberger U. Regressed retinopathy of prematurity: the relationship between clinical risk factors of the newborn period and regressed retinopathy of prematurity severity in a preterm born population of Stockholm county 1976-81. *Acta Paediatr.* 1992;81:103-106.
3. Kalina RE. Treatment of retinal detachment due to retinopathy of prematurity. *Ophthalmology.* 1991;98:3-4.
4. Kalina RE. Letter to editor. *Ophthalmology.* 1991;98:1149.
5. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, Tung B, The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology.* 1991;98:1628-1640.
6. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome—structure and function. *Arch Ophthalmol.* 1990;108:1408-1416.
7. U.S. Congress, Office of Technology Assessment. Neonatal intensive care for low birth weight infants: costs and effectiveness. Health Technology Case Study 38. Washington, DC;1987.
8. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics.* 1991;87:587-597.
9. Wegman ME. Annual summary of vital statistics-1991. *Pediatrics.* 1992;90:835-845.
10. Wegman ME. Annual summary of vital statistics-1981. *Pediatrics.* 1982;70:835-843.
11. Bose C, Corbet A, Bose G, Garcia-Prats J, Lombardy L, Wold D, Donlon D, Long W. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. *J Pediatr.* 1990;117:947-953.
12. The Committee for the Classification of Retinopathy of Prematurity. An international classification for retinopathy of prematurity. *Arch Ophthalmol.* 1984;102:1130-1134.
13. Greve PA. Retinopathy of prematurity: current risk management issues. Perspectives in Healthcare Risk Management. Summer 1992:9-12.
14. Kendig JW, Notter RH, Cox C, Aschner JL, Benn S, Bernstein RM, Hendricks-Munoz K, Maniscalco WM, Metlay LA, Phelps DL, Sinkin RA, Wood BP, Shapiro DL. Surfactant replacement therapy at birth: final analysis of a clinical trial and comparisons with similar trials. *Pediatrics.* 1988;82:756-762.

➤ *Continued on page 22*